CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-278

MICROBIOLOGY REVIEW

Micro KW #1

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REVIEW TO HFD-617
OFFICE OF GENERIC DRUGS
MICROBIOLOGY STAFF
MICROBIOLOGIST REVIEW OF AN ANDA
3 June 1999

A. ANDA 75-278

PRODUCT NAME: PACLITAXEL INJECTION, 6 mg/mL

APPLICANT: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

INNOVATOR DRUG PRODUCT: TAXOL BY BRISTOL-MYERS SQUIBB
(NDA 20-262)

DOSAGE FORM: For Injection in 30-mg/5 mL (6 mg/mL)
METHOD OF STERILIZATION: [redacted]
PHARMACOLOGICAL CATEGORY: Anticancer Agent

B. INITIAL APPLICATION DATE: 19 December 1997 (subject of this review)
DATE OF AMENDEMENTS: 21 January 1998
23 March 1998
26 April 1998
26 August 1998
23 April 1999 (subject of this review)

ASSIGNED FOR REVIEW: 29 April 1999

RELATED DOCUMENTS:

DMF NUMBER	MANUFACTURER	COMPONENT
[redacted]		

C. REMARKS: A consult was requested from the OGD to review the sterility assurance information in this ANDA. The active ingredient of the drug product is paclitaxel and is the same as that in the reference listed drug. Paclitaxel is obtained via [redacted] process from *Taxus brevifolia*.

Paclitaxel Injection is supplied as a sterile nonaqueous solution intended for dilution with a parenteral fluid prior to intravenous infusion.

D. CONCLUSIONS: The ANDA 75-278 is not recommended for approval from the standpoint of product quality microbiology. Please see section E for Review Notes and Section F.

/S/ 3/June/99

Patricia F. Hughes, Ph. D.
Review Microbiologist

/S/ 6/7/99

/S/ 6/10/99

cc.: Original ANDA 75-278
HFD-160 /Consult File
HFD-805/PFHughes
HFD-617/DivFile
HFD-617/Beers Block
Drafted by PFHughes, 3 June, 1999
R/D Initialed by PHCooney

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ON ORIGINAL

E. REVIEW NOTES:

The quantitative composition of the drug product is as follows:

Components	Mg per mL	— per batch — vial	— per batch — vial
Active component Paclitaxel	6.0	—	—
Inactive components			
Dehydrated Alcohol, USP	—	—	—
— Castor Oil, NF —	527 —	—	—
Sodium Metabisulfite, NF	—	—	—
Sterile Water for Injection, USP	—	—	—
Total theoretical Weight	931.8	—	—

The finished dosage form will be manufactured, processed, packaged and labeled at The University of Iowa, Division of Pharmaceutical Service, 20 Pharmacy Building, Iowa City, Iowa, 52242-1112. The finished dosage form will be release and stability tested at Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730. — testing will be conducted at — , in —

E.1. Building and Facilities

Rooms labeled — on the floor plan of the Pharmaceutical Service of the University of Iowa are used for the manufacture of sterile products and a floor plan is provided in Appendix A of volume 1.2. The floor plan of the facility is adequate. The

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Office of Generic Drugs, HFD-620
Microbiology Review #2
May 8, 2000

A. 1. ANDA: 75-278

APPLICANT: Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

2. PRODUCT NAME: Paclitaxel Injection, 6 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/mL as a 5-mL fill in a 5-mL single-use vial; Intravenous Injection.

4. METHOD OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

B. 1. DATE OF INITIAL SUBMISSION: December 19, 1997

2. DATE OF AMENDMENTS:
April 23, 1999
January 13, 2000; Received January 14, 2000 **(Subject of this Review)**

3. RELATED DOCUMENTS:
DMF [redacted]
DMF [redacted]
DMF [redacted]
NDA 20-262 – Bristol-Myers Squibb (innovator product, Taxol®)

4. ASSIGNED FOR REVIEW: April 28, 2000

C. REMARKS: The subject drug product is manufactured by the University of Iowa Division of Pharmaceutical Services in Iowa City, Iowa. Release and stability testing is conducted by Mylan Pharmaceuticals in Morgantown, WV.

Microbiology Review #1 was completed as a consult to the Office of Generic Drugs by Dr. Patricia Hughes at the time with the Office of New Drug Chemistry (CDER/FDA).

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. REVIEW NOTES".

/S/

5/10/2000

Paul C. DeLeo, Ph.D.

/S/ 5/10/00

c: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by P. DeLeo, HFD-600; V:\MICROREV\75278MR2.DOC
Initialed by A. High

/S/ 5/11/00

APPEARS THIS WAY
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OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
May 21, 2001

A. 1. **ANDA 75-278**

APPLICANT: Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

2. PRODUCT NAME: Paclitaxel Injection, 6 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/mL sterile, non-aqueous solution for intravenous administration supplied as a multiple-dose formulation and packaged in 100 mg/16.7 mL (20 mL vial) and 300 mg/50 mL (50 mL vial) formulations.

4. METHOD(S) OF STERILIZATION: [redacted] followed by aseptic filling

5. PHARMACOLOGICAL CATEGORY: Anti-Neoplastic

B. 1. DATE OF INITIAL SUBMISSION: December 19, 1997

2. DATE OF (GRATUITOUS) AMENDMENT: September 29, 2000
Subject of this Review (Received October 3, 2000)

3. RELATED DOCUMENTS: January 13, 2000 submission-Vol. 4.1

4. ASSIGNED FOR REVIEW: May 17, 2001

C. REMARKS: The subject drug product Paclitaxel Injection, 6 mg/mL is manufactured by the University of Iowa, Division of Pharmaceutical Services in Iowa City, Iowa. Release and stability testing is conducted by Mylan Pharmaceuticals in Morgantown, WV. The product is [redacted]. This submission includes 2 additional package sizes of 100 mg/16.7 mL in a 20 mL vial and 300 mg/50 mL in a 50 mL vial. The January 13, 2000 microbiology submission has been reviewed and recommended.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance.

Specific comments regarding the [redacted] process are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/s/ 5/21/01

Marla Stevens-Riley, Ph.D.

/s/ 5/21/01

cc: Original **ANDA**
Duplicate ANDA
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Field Copy
Drafted by M. Stevens-Riley, HFD 600 v:microrev\75-278a
Initialed by M. Fanning/A. High

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OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
May 31, 2001

A. 1. **ANDA 75-278**

APPLICANT: Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

2. PRODUCT NAME: Paclitaxel Injection, 6 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/mL sterile, non-aqueous solution for intravenous administration supplied as a multiple-dose formulation and packaged in 100 mg/16.7 mL (20 mL vial) and 300 mg/50 mL (50 mL vial) formulations.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Anti-Neoplastic

B. 1. DATE OF INITIAL SUBMISSION: December 19, 1997

2. DATE OF FAX AMENDMENT: May 30, 2001
Subject of this Review (Received May 30, 2001)

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: May 31, 2001

C. REMARKS: The subject fax amendment provides for the response to the Microbiology Deficiencies dated May 24, 2001.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. Review Notes".

/S/ 5/31/01
Marla Stevens-Riley, Ph.D.

5/31/01

E. REVIEW NOTES:

The applicant has responded to the Microbiology Deficiencies in the letter dated May 24, 2001. The original questions are italicized.

1. *Please provide an Anti-microbial Preservative Effectiveness Test for multiple-dose use of the subject drug product.*

Response:

The applicant states that the APET has been performed by [redacted] a [redacted] referenced in the original application. The test results indicate that the subject drug product meets USP 24 <51> requirements. The test results from [redacted] are provided on page 15.

Acceptable

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Microbiology Comments to be Provided to the Applicant

ANDA: 75-278 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Paclitaxel Injection, 6 mg/mL (100 mg/16.7 mL and 300 mg/50 mL)

Microbiology Deficiency

Please provide an Anti-microbial Preservative Effectiveness Test for multiple-dose use of the subject drug product.

Please clearly identify your amendment to this facsimile as □RESPONSE TO MICROBIOLOGY DEFICIENCIES□. The □RESPONSE TO MICROBIOLOGY DEFICIENCIES□ should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

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